Physics of biological tissues

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COLLÈGE DE FRANCE 1530

institutCurie Together, let's beat cancer.

Outline

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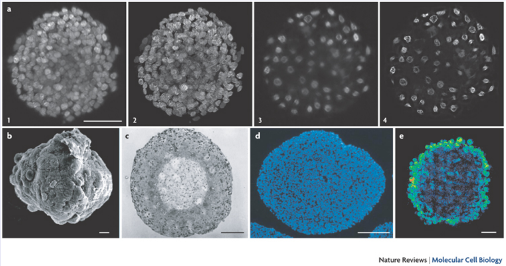
1. *Active matter*
2. *Tissue Monolayers with nematic order*
    - Defects in nematic tissue monolayers
    - Spontaneous flow
3. *Multicellular spheroids*

Multicellular spheroids



Intestinal epithelia


Figure 11-5a The Biology of Cancer (© Garland Science 2007)

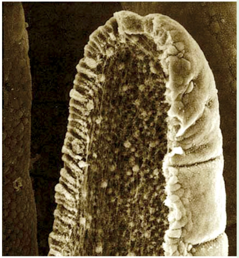
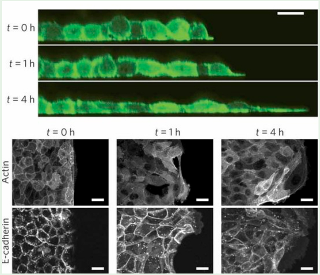


Figure 11-5b The Biology of Cancer (© Garland Science 2007)

Confluent monolayers



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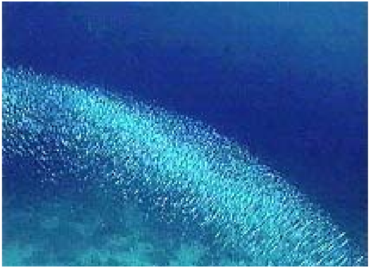
Active Systems

- Tissues
- Bacterial colonies Kessler, Goldstein
- Vibrated granular materials Menon et al.
- Active colloids, Active nematics Ramaswamy et al.
- Bird flocks, Fish shoals Vicsek, Toner, Chaté, Carere



- Marchetti et al, Rev.Mod.Phys. 2013

Cell division and Homeostatic pressure

Cell division and apoptosis

- Division rate $k_d(\rho, \text{biochemical state})$
- Apoptosis rate k_a $\frac{\partial\rho}{\partial t} + \partial_\alpha(\rho v_\alpha) = (k_d(\rho) - k_a(\rho))\rho$

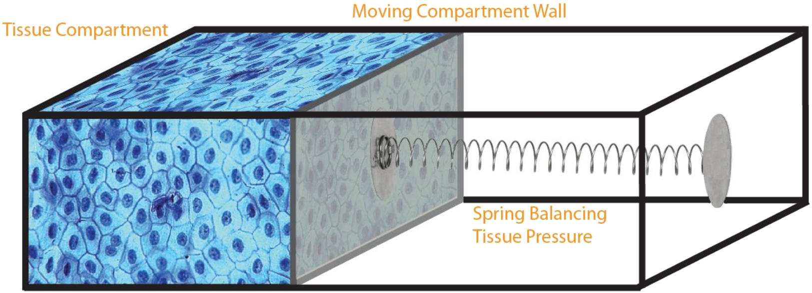
Tissue Pressure

- Pressure exerted by the cells
- Division rate k_d decreases with pressure
- Apoptosis rate k_a increases with pressure

Homeostatic pressure

- Steady state pressure of a tissue P_h
- $k_d - k_a(P_h) = 0$

Homeostatic Pressure Basan



- Permeable compartments
- Fluctuations due to cell divisions

Cell division and Homeostatic pressure

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Constitutive equations of an isotropic tissue J. Ranft

"Shear" stress

- Elastic stress $\tilde{\sigma}^{el}_{\alpha\beta} = 2Eu_{\alpha\beta}$
- Stress relaxation by oriented cell divisions Fink
- Total stress

$$\frac{d\tilde{\sigma}_{\alpha\beta}}{dt} + \frac{\tilde{\sigma}_{\alpha\beta}}{\tau_a} = 2E\tilde{v}_{\alpha\beta}$$

- Maxwell viscoelastic model with relaxation time $\tau_a \sim 1/k_d$
- Shear viscosity $\eta \sim Ek_d^{-1}$

Pressure Relaxation

- Near homeostatic condition $(k_d - k_a)(\rho) = -\frac{1}{\tau}\frac{\delta\rho}{\rho}$
- Stress relaxation to homeostatic pressure $-P_h$
- Infinitely compressible system with large fluctuations

Active liquid behavior of polarized tissues

Polarized tissues

- Cells aligned along a direction $\mathbf{p}$
- Orientational tensor $q_{\alpha\beta} = \langle p_\alpha p_\beta - \frac{1}{d}\delta_{\alpha\beta}\rangle$
- Spontaneous orientation $q^0_{\alpha\beta}$

Active behavior of tissues

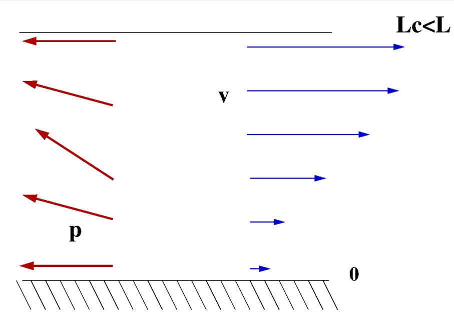
- Orientation by stress $\tilde{\sigma}_{\alpha\beta} = \sigma_0(q_{\alpha\beta} - q^0_{\alpha\beta})$
- Constitutive equation $(1 + \tau_\mathrm{a}(\mathrm{D}/\mathrm{D}t))\tilde{\sigma}_{\alpha\beta} = 2\eta\tilde{v}_{\alpha\beta} - \zeta\Delta\mu\tilde{q}^0_{\alpha\beta}$
- Active stress

Active Matter

- Energy consumption at local scale
- Orientational order
- Fluid-like behavior

Spontaneous flow Frederiks transition

Parallel anchoring conditions



Flow bifurcation R.Voituriez

- Same anchoring condition on both surfaces
- Active stress equivalent to an external magnetic field along x axis
- Instability for a finite thickness

$$L_c = \left(-\frac{\pi^2 K(\frac{4\eta}{\gamma} + (\nu+1)^2)}{2\zeta\Delta\mu(\nu+1)} \right)^{1/2}$$

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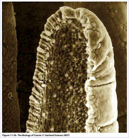
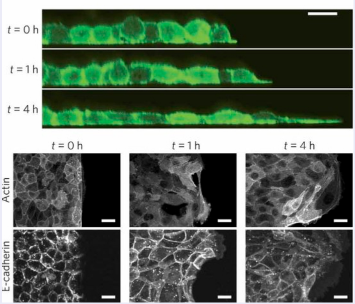
Examples of tissue monolayers

Intestinal epithelium



Confluent Layers on a solid substrate Trepat

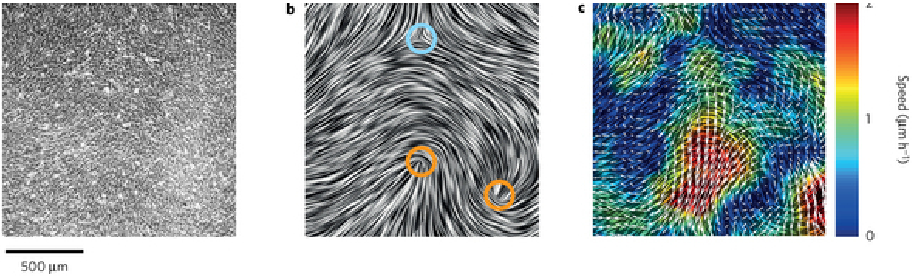


Outline

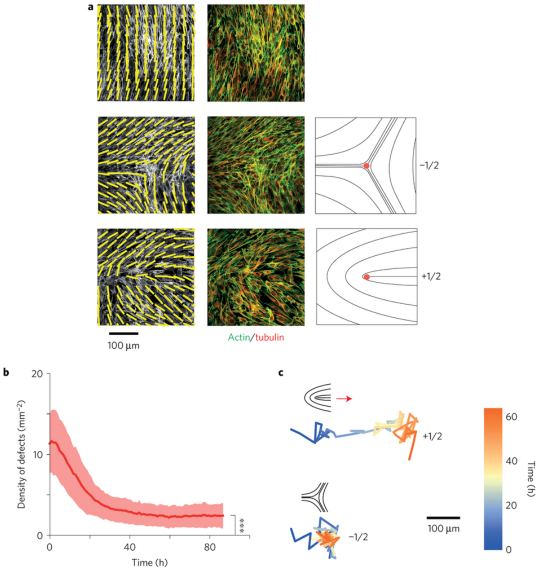
Confluent elongated cells G. Duclos, P. Silberzan

Nematic order of Spindle shaped cells

- Spindle-shaped cells: NIH 3T3, RPE1, C2 C12
- Elongated cells show nematic order: head-tail symmetry
- Different defects expected for polar and nematic cells
- Spontaneous cell flow due to activity
- Defect motion



Defect motion in cell monolayers

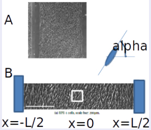


- Only $+1/2$ and $-1/2$ defects
- Spontaneous motions of $+1/2$ defects
- $-1/2$ defects do not move
- Annihilation between $+1/2$ and $-1/2$ defects

Outline

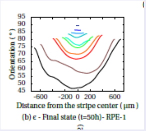
Spontaneous tissue flow G. Duclos, V. Yashunsky, P. Silberzan

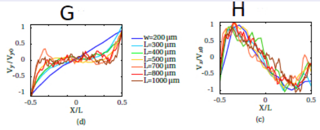
Experiment

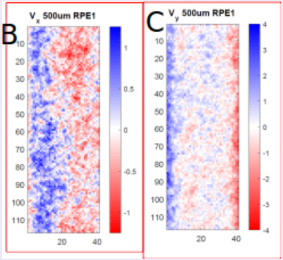


- Stripe width 50μm to 800μm
- Cell orientation
- PIV

Velocity and cell orientation



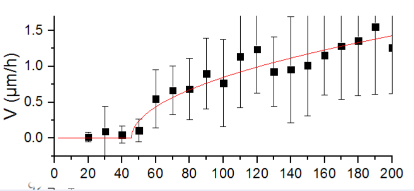




Active gel theory C. Blanch-Mercader

Spontaneous flow

- Fredericks transition



Theoretical developments

- Substrate friction: screening length $\lambda = \left(\frac{4\eta+\gamma(\nu+1)^2}{\xi}\right)^{1/2}$

$$\frac{1}{L_c^2} = \frac{1}{L_c^2}(\xi = 0) - \frac{1}{\lambda^2}$$

- Transverse flow related to cell division L. Brézin
- Chiral effects

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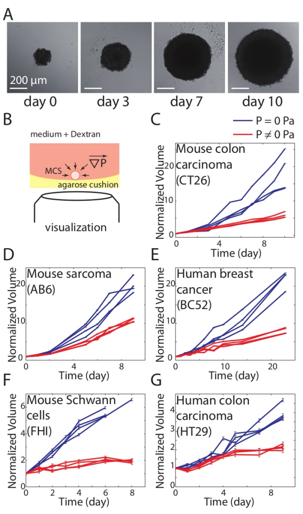
F. Brochard

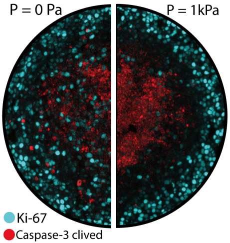
Spheroid growth F.Montel, M.Delarue

Growth experiments

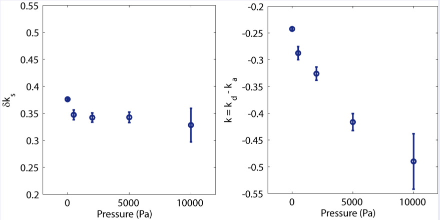


- Indirect experiments
  - Dialysis bag
  - Pressure exerted by dextran
- Direct experiments
  - Spheroid in contact with dextran solutions
  - No penetration of dextran in spheroid

Surface growth



Pressure dependence

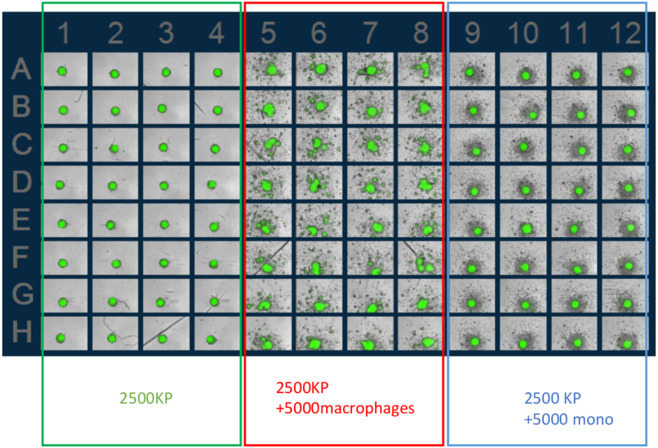


$$\partial_t V = (k_d - k_a)V + 4\pi\left(\frac{3}{4\pi}\right)^{2/3} \delta k_s \lambda V^{2/3}$$

- Nutrient effect

Elgeti

Interaction spheroid-macrophages *P. Benaroch, J. Nikolic*



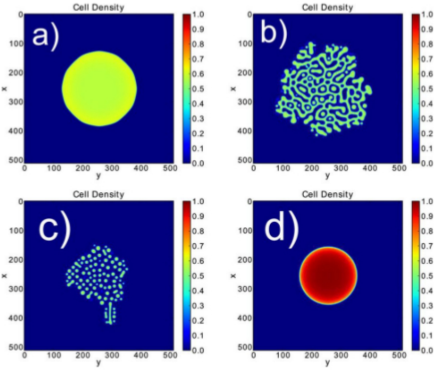
Multicomponent spheroid *M. Benamar, J. Ackermann*

- Cancer Immunotherapy
- Cancer cells, Interstitial fluid and extracellular matrix, Dead cells

Heterogeneous spheroid

Spinodal decomposition

- Interacting components, effective free energy for two components
- Include cell division
- Unstable composition inside the spheroid
- 3 component systems; non dividing macrophages



he stepsize dx is 0.12, the steptime is 10^{-4}. The same expression for Σ is chosen for all pictures, p = 2 and $\phi_e = 0.6$. Different

Summary

- Tissues as active nematic liquids
  - Defect dynamics
  - Spontaneous flow
  - Multicellular spheroids

-
  - Spheroid instabilities due to macrophages
  - Multicomponent tissues and phase separations
  - Cell extrusion from monolayers and 3 dimensional tissues
  - Transverse orientational fields
  - Coupling to population dynamics and genetics